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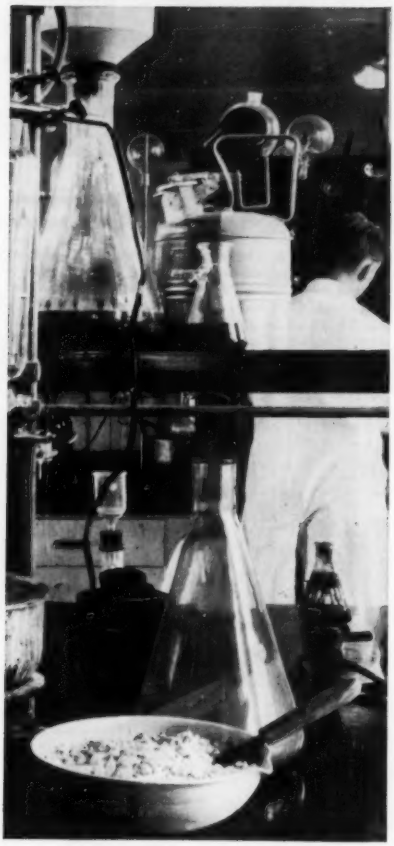

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E D I T O R I A L

WHICH ORGANIZATION REPRESENTS THE PROFESSION OF PHARMACY?

SOME little time ago, we volunteered to suggest that the qualifications for membership in one of our national organizations for pharmacy were entirely too lax and, possibly, almost meaningless. This caused considerable controversy and even led to a heated debate before the House of Delegates of that organization at its 1958 convention. A committee was subsequently appointed to study the needed changes in the qualifications for membership and such committee is expected to make a report and recommendations at the next annual convention.

We do not at this time wish to go into detail concerning what we feel is wrong with the requirements for membership in the American Pharmaceutical Association. We do wish to point out again, as it has been done many times before by those who have analyzed pharmacy's organizational problem, that the structure of pharmacy in the United States is such that the organized confusion that now prevails can hardly be unexpected. There is no calling or profession in the United States, to the best of our knowledge, which has so many organizations, so many competing organizations, or so many organizations constantly at cross-purposes. It is small wonder that those who would obstruct our professional objectives or harm us economically, or do any other thing contrary to our interests find it such a relatively simple task. It would almost seem that things have been organized this way purposely for it is difficult to imagine a group of individuals presumably having a common purpose who are less effective in carrying it out.

We wish to outline one of the critical problems which must be solved if organized pharmacy is ever to succeed in gaining for itself the place and prestige which it deserves. First, we must have an integrated organization of pharmacy just as does medicine. At the

present time, it is not difficult to find local pharmaceutical organizations, such as those within a city, at loggerheads with the county or state pharmaceutical association, and vice versa. On the surface, it would appear that these organizations are voicing differences based upon entirely different concepts of what is best and proper for the profession. Underneath the surface, it is often found that they are competing for members and operating on the theory that a pharmacist cannot afford to belong to both and, thus, the competition. It often evolves into a personal feud between the individuals who are the key figures within each organization—usually career men—whose success and fortune depend upon the financial success of the organization. This same sort of competition has been seen in the past even between our national organizations in pharmacy; only too often they have had serious differences of opinion when, in fact, there should have been unanimity and concerted effort.

The most serious fault to be observed in our national pharmaceutical associations is that one is much too restrictive in its membership to represent the profession of pharmacy since it admits only owners of retail drugstores while the other is too all inclusive in its membership taking any and sundry that profess any interest whatsoever in pharmacy even in some of its most crass commercial forms.

One cannot help but ask just who, indeed, represents the pharmacist as the American Medical Association represents the physician. Critics will say, "But pharmacy is so heterogeneous," and, of course, it is. It so happens, however, that each of the specialized areas of pharmacy has its own special organization. Thus, we have the Pharmaceutical Manufacturers Association representing the manufacturers, the National Wholesale Druggists' Association and the Federal Wholesale Druggists' Association representing wholesalers, the National Association of Retail Druggists representing retailers, and we could go on. Some very sincere and well-intentioned people believe that the A. Ph. A. should be an over-all umbrella, so to speak, embracing and covering every avenue of pharmacy and, indeed, we may need such an organization. If, however, this is its proper function, then we reiterate the question, "Who represents the profession of pharmacy?" Since the answer to this is not evident, we follow with the question, "Does the profession not need representation?" In our present scheme of things, it is unthinkable that any group comprising well over 100,000 people with a similar academic and professional background, similar

professional instinct, and with a grossly underprivileged status does not need representation. It is small wonder that so many pharmacists seem at times discouraged and know not where to turn. Can it be that they have been kept in their present state by deliberate design? There are those who may indeed benefit greatly from the present state of disorganization from which the profession suffers.

Unless some effective means is found to organize the practicing pharmacists of America into a well-knit, smooth-functioning professional organization, the time may soon come when the present vacuum will be filled by the growth of unionism already on the national scene. The present *status quo* is intolerable to many pharmacists who would, we fear, gladly sell their professional birthright rather than remain forever weak and disorganized. American pharmacy needs immediate dramatic action. Will it be too little and too late?

L. F. Tice

MORE DRUGS DIE YOUNGER AS MORE PEOPLE LIVE LONGER *

By David D. Stiles **

"EXPLOSIVE" is a more apt description of the 1958 prescription market than is "dynamic," a term frequently used to characterize it. For, during 1958, there truly was an explosion in the profitable group of prescription products—those appearing 5 or more times per 10,000 prescriptions.

More products, far more, dropped out of this group and many more products entered it than during any previous year. In both cases, the products involved were younger than those observed in other years.

Two forces are responsible for this trend:

First, the keen competitive research race to produce new and more effective drugs to alleviate suffering and lengthen the life span.

Second, modern "crash" promotional programs that create almost immediate acceptance and prescription demand.

We are in the tenth year of studying the prescription market. Each year, we scrutinize more than a quarter million prescriptions. This has been possible only through the cooperation of the pharmacy schools—their deans, faculty supervisors, and hundreds of students—and pharmacists in twenty-three states or populous areas.

Each year, we have observed a parade of products into and out of the group of products prescribed 5 or more times per 10,000 prescriptions. In 1958, the parade was longer. (Hereafter, the products prescribed 5 or more times per 10,000 prescriptions will be referred to as the 400 Group.)

This study has led us to some significant conclusions about what is taking place in the prescription market. These conclusions may not differ from opinions and generalizations that have been expressed previously, but they have a statistical basis. After listing our conclusions, we will present a two-minute statistical study of the three

* Presented before the Pharmaceutical Economics Section, American Pharmaceutical Association Convention, August 1959 and published in *Modern Medicine*, September 1959.

** Director of Market Development, Abbott Laboratories.

CHART I

NUMBER OF PRODUCTS PRESCRIBED AT A RATE OF FIVE OR MORE PER 10,000 ℞'s

(1952-1958)

Year	*Number of Products*
1952	404
1953	393
1954	398
1955	404
1956	408
1957	395
1958	408

sub-groups; that is, the products dropping out, the products entering, and the products remaining in this profitable 400 Group. We are also supplying with this paper, charts showing the statistical computations upon which these data are based. We will not take the time to review these charts. They are made available for your further study, if you are interested.

Here are our conclusions:

1. As pharmaceutical research expands, the turnover of products leaving and entering the 400 Group increases.

2. This turnover in 1958 was much higher than we have ever observed in our ten-year study of the prescription market.

3. The products entering and leaving the 400 Group are younger, indicating more rapid obsolescence.

4. Despite this increased turnover, the number of products in the 400 Group remains constant. This is phenomenal since there are 400 to 500 products introduced each year. There are said to be about 1,200 products under more or less heavy promotion. But, in nine years, the number prescribed at this high frequency has ranged only between 393 and 413. For 1958, it was 408.

5. The products dropping out are replaced by products with much higher prescription frequency and dollar volume.

6. About the same number of companies are represented annually by the products that drop out and enter the 400 Group. (See discussion of these sub-groups.)

7. Products which remained at this prescription frequency through 1957 and 1958 accounted for the bulk of the prescription market (about 73.5 per cent of the dollar volume), but their prescription frequency rate and dollar volume showed a decline from 1957. Many of these products are headed for obsolescence.

8. In 1958, a higher percentage of products introduced during the year reached and maintained a frequency of 5 or more per 10,000 prescriptions. In the past years, we have observed that only 3 per cent to 4 per cent of these new products reached this frequency during the year of their introduction. However, in 1958 this percentage was more than doubled, based on the published report of Mr. Paul de Haen, who listed 370 new chemical entities and combinations for the year.

9. Our studies substantiate the belief of many that, as effort and expenditures for pharmaceutical research increase and as crash promotional programs continue to publicize the results of this expanded research, we can anticipate even greater annual turnover of prescription products with acceleration in their rate of obsolescence.

10. While the rapidity of obsolescence was slightly greater in certain therapeutic groups, nearly all therapeutic groups contributed to this obsolescence.

CHART II

AGE OF PRODUCTS BY SUB-GROUPS

1958

Category and Number of Products	*Three Years Old or Less*		*Five Years Old or Less*		*Ten Years Old or Less*		*Over Ten Years Old*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Dropping Out (69)	13	18.8	33	47.8	51	73.9	18	26.1
Entering (82)	61	74.4	70	85.4	74	90.2	8	9.8
Remaining (326)	18	5.5	111	34.0	194	59.5	132	40.5

Note: The age is given since introduction. As products Dropping Out did not reach 5 or more per 10,000 prescriptions in 1958, the thirteen in the "Three Years Old or Less" category actually maintained this rate only two years or less. The 47.8% of the products five years old or less maintained the rate only four years or less, etc.

There are two slight possibilities of error in our computations which I would like to clarify. One, the rate at which products are prescribed is based on their appearances in new prescriptions. In the case of compounded prescriptions, credit for appearance goes to each component. Since compounded prescriptions probably were less than 5 per cent of the total and since most ingredients were official drugs, this should not cause any appreciable error.

The other possibility of error is in the 40 per cent figure we used for refills. This is a little lower than most recent figures. Narcotics, antibiotics, barbiturates, and others do not have 40 per cent refills. But, on the other hand, we are not dealing with these products individually in this paper. Many products in these groups far exceed 40 per cent in refills, so it is our belief that the one will offset the other.

We should also like to define the use of the word "product." We apply the word product to any single brand or official name, segregating all strengths and forms prescribed under that name, if administered by the same route. That is, all oral forms and strengths would be combined but, if the same product were used topically and as an ophthalmic, it would be considered separately.

Let us look first at those products that dropped out of the 400 Group in 1958. There were sixty-nine such products—more than we have ever observed in previous studies. In fact, there were 72 per cent more than what we have considered normal—30 to 40 products. These sixty-nine products are 17.4 per cent of the 395 which were in this Group in 1957.

CHART III

FREQUENCY RATE AND DOLLAR VOLUME FOR PRODUCTS PRESCRIBED FIVE OR MORE TIMES PER 10,000 ℞'s

1958

Category and Number of Products	*Rate Per 10,000 ℞'s*	*Projected Dollar Volume*
Dropping Out (69)	243	$47,543,085
Entering (82)	1,304	$330,693,395*
Remaining (326)	7,353	$1,326,457,215

* Computed for twelve months, although many products were not on the market for the entire year.

While these sixty-nine products that appear to be heading for obsolescence maintained a rate of well over 5 per 10,000 prescriptions in 1957, they dropped to a total frequency of 243.3 per 10,000 prescriptions in 1958, or a per product frequency of 3.5 per 10,000 prescriptions. Their dollar volume for the past year is estimated at $47,500,000. The products that entered this Group and replaced these sixty-nine, as we will show, had more than five times the prescription frequency and more than seven times the dollar volume.

The sixty-nine products that dropped out were not limited to any one or even a few therapeutic groups. They dropped out of thirty-six of the ninety-five therapeutic categories which we list. Eight of them were corticoids which were, of course, replaced by newer corticoids. Seven were antibiotics or antibiotic combinations. Six were antispasmodics and anticholinergics, and four were antihistamines. Others were distributed in such groups as nutritionals, hematinics, cough and cold preparations, and sulfas, etc.

Nineteen per cent of the products that dropped out were less than three years old; forty-eight per cent were less than five years old, and seventy-four per cent or nearly three quarters were less than ten years old. Twenty-six per cent were between five and ten years old, and six products (or nine per cent) antedated 1900.

Not all of these sixty-nine products are headed for immediate obsolescence though. We have a few products—probably five or six—that are "in-and-outers." They drop below the 5 per 10,000 prescriptions rate one year and, through a splurge of advertising or promotion, get back into the Group the following year but, for the most part, the products that drop out are following a pattern of decline.

It should also be mentioned in this connection that, while some of these products have declined on prescription, their over-the-counter sales have increased, so their total volume may have expanded despite a decline in their use on prescription.

CHART IV

PRODUCTS REMAINING IN "400 GROUP" THROUGHOUT 1957 AND 1958

Number of Products	*Rate Per 10,0000 Rx's*		*% Change*	*Dollar Volume (In Billions)*		*% Change*
	1957	*1958*	*57/58*	*1957*	*1958*	*57/58*
326	7,752	7,353	—4.0	$1.403	$1.326	—5.5

Twenty-eight companies were represented by these declining products. One of these twenty-eight companies had seven of the sixty-nine products; another, six; and another, five. There were also two companies that had four products leave the 400 Group and three companies that had three products drop out.

Our interpretation of the reasons for the unusually large number of descending products for the three top companies is that they currently introduced one or more extremely high volume products which have taken the place of products that they had in the 400 Group. Also, some of these new high volume products may have detracted from the promotion of the declining products thus accelerating their obsolescence.

Next, let us look at the eighty-two products, represented by thirty-eight companies, which entered the 400 Group in 1958. Possibly a word of explanation is necessary because not all of these products were on the market throughout 1958. In fact, 41.5 per cent of these eighty-two products were less than a year old. Seventy-one per cent were less than two years old, and 85.4 per cent less than five years old.

This confirms statistically what we have suspected to be true: that the impact of our modern "crash" promotional programs creates an almost instantaneous acceptance which immediately results in a high prescription frequency for the product—or else the promotional program fails and the product is doomed to mediocrity or less. There are exceptions, of course, but you will find that most of the 11 per cent that are older than five years are these "in-and-out" products that have been previously discussed.

No product introduced during the year 1958 was added to this group of high prescription frequency products unless for several months it had demonstrated a frequency well in excess of 5 per 10,000 prescriptions. In projecting the contribution of these products to the prescription market, we have projected their sales frequency rate on a twelve-month basis.

We believe that these projections are conservative. Some of these products may have reached a peak and are now headed for a decline because of replacement, diminished promotional support, or some other reason. Many, however, are showing month-by-month increases in their rate of appearance.

In prescription frequency, these eighty-two products entering the 400 Group total 667.4 per 10,000 prescriptions, or about 6.7 per cent of the total new prescriptions. In dollar volume, projected for a year, they represent $330,000,000 in prescription sales, or 18.3 per cent of the estimated dollar volume of the prescription market in 1958.

These data on the high dollar volume of new products would tend to confirm for the entire industry a statement made in the past year by the head of one of the largest pharmaceutical manufacturers—"Forty per cent of our sales last year came from products introduced in the last five years."

Quite interesting was the fact that three companies had seventeen products entering the "400 Group," and the same three companies had seventeen products dropping out of the Group. What is even more interesting is the fact that the dollar volume of the seventeen products entering was 9.9 times the dollar volume of the products dropping out.

CHART V

THERAPEUTIC GROUP IN WHICH GREATEST CHANGE OCCURRED IN 1958

Therapeutic Group	*No. Products Dropping Out*	*No. Products Entering*	*No. Products Change 57/58*
Analgesics	5	4	—1
Antibiotics	8	17	+9
Antihistamines	4	4	Unchanged
Antispasmodics and Anticholinergics	6	4	—2
Ataractics	2	6	+4
Cardiac, Including Rauwolfias	6	—	—6
Corticoids	8	8	Unchanged
Cough and Cold	9	4	—5
Muscle Relaxants	2	5	+3
Sulfas	5	3	—2
Total	55	55	

Now let us turn a critical eye on those 326 products that maintained a rate of 5 or more per 10,000 prescriptions throughout both 1957 and 1958. In 1958, they represented a frequency rate of 7,353 per 10,000 prescriptions, or about 73.5 per cent of the prescriptions filled. In prescription dollars, they represented 72 per cent of the dollar volume.

Let us see what happened to them as a group in 1958. Based on slightly increased prescription market for 1958, they dropped 4 per cent in their frequency rate—from 77.5 per cent in 1957 to 73.5 per cent in 1958. In dollar volume, they dropped 5.5 per cent, from $1,403,000,000 in 1957 to $1,326,000,000 in 1958.

CHART VI

PRODUCT STUDY BY COMPANY
FOURTEEN LEADING MANUFACTURERS

1958

Number of Products, "400 Group"

Company	*Remaining Jan. 1, 1958*	*Entering*	*Dropping Out*	*Balance Jan. 1, 1959*	*Product Change 57/58*
A	15	6	7	14	—1
B	11	5	6	10	—1
C	9	2	5	6	—3
D	11	6	4	13	+2
E	10	1	4	7	—3
F	6	2	3	5	—1
G	7	4	3	8	+1
H	10	None	3	7	—3
I	26	3	1	28	+2
J	21	6	2	25	+4
K	15	1	1	15	Unchanged
L	11	3	2	12	+1
M	11	3	2	12	+1
N	10	3	1	12	+2

7 Increase *6 Decrease* *1 Unchanged*

Net increase for products in the 400 Group by these fourteen companies equals one.

Of these 326 products, 60 per cent were introduced in the past ten years and represented a frequency rate of 4,454 per 10,000 prescriptions or 44.5 per cent of total new prescriptions. In dollar volume, these products represented 53 per cent of all prescription dollar sales.

Now, if we put together the 326 products we carried over from 1957 through 1958--that is, those less than ten years old—and add to that the products—also less than ten years old—that attained this frequency in 1958, we find that they constitute 57.1 per cent of all prescriptions filled, and account for 72.4 per cent of the prescription dollar volume for all products appearing 5 or more times per 10,000 prescriptions.

From previous studies, we can assume that about the same percentages, based on product age, apply to the great number of products with a prescription frequency of less than 5 per 10,000 prescriptions.

This array of statistics leads us to some specific conclusions that confirm general accepted hypotheses. One such conclusion is that the fate of most new products is determined in a matter of weeks or months. Even though they may catapult into high positions of prescription frequency, their life expectancy is being constantly reduced.

We conclude, too, that fortunately for inventory purposes these products, like old soldiers, do not die, they fade away. But, that they eventually do fade is attested to by the fact that year after year, in our studies of more than a quarter million prescriptions, we find that we are dealing with about the same number of products despite the annual invasion of new products.

Summary

Acceleration of pharmaceutical research, producing more and more drugs and combinations of drugs that alleviate suffering and prolong life, also accelerates the rate of obsolescence of prescription drugs. This is axiomatic.

It would be useless to express this in terms of average product longevity. Too many factors affect too many drugs individually. Often, a new drug that appears destined to have a long life may suffer an early decline due to the introduction of a newer drug of proven superiority to replace it.

But we do know this: Whereas a decade ago or so it took two or three years or more for prescription products to reach a high peak

of prescription frequency, today, in most cases, their fate can be foretold in a matter of months. Sometimes, this is obvious by the second or third month; usually, it occurs within five to seven months.

A few years ago, it was true that, once a prescription product reached a high frequency peak, it had a good chance of remaining at a high level of prescription frequency for five or ten years or more. Today, it may start downward toward oblivion in three to five years, or even sooner. The descent is sometimes sudden. Sometimes, it is slow. It is unpredictable.

However, from the statistics we have developed, particularly those from the 1958 prescription market, it is obvious that the life expectancy of prescription drugs has been shortened as man's life expectancy has been lengthened. And the trend is definitely toward shortening further the life span of prescription drugs.

Lord Kelvin once said, "When you can measure what you are speaking about and express it in numbers, you know something about it. But when you cannot, your knowledge is of a meagre and unsatisfactory kind."

In this paper, we have simply tried to express in numbers what occurred in the prescription market in 1958.

PHOSPHORAMIDES IN THE MANAGEMENT OF LEUKEMIA

By John R. Sampey *

PHOSPHORAMIDES are among the most promising of the newer chemotherapeutic agents in the management of the leukemias (13-16). A review of the current literature on the use of TEPA (triethylene phosphoramide), DEPA (diethylene phosphoramide), Thio-TEPA (triethylene thiophosphoramide), and OPSPA (oxapentamethylenediethylene thiophosphoramide) shows an over-all remission rate of 72 per cent in 121 cases. The number of clinical trials on each of the five types of leukemia presented in this study is too limited for statistical purposes, but the data do serve as valuable screening tests for further evaluation.

Chronic Myelocytic Leukemia. Phosphoramides have been tested more extensively on chronic myeloid leukemia than on any other type. Koyama (6) described 6 objective remissions in 8 patients on Thio-TEPA therapy, and Shay (17) noted good clinical and hematologic remissions in 4 of 7 patients, with limited response in the 3 remaining cases. Kimura (5) classed only one of his 5 remissions as good on this drug, and 2 of the 7 cases showed no response. Winkler (24) obtained hematic remissions of 2 and 2½ months in 2 of 4 patients, but one turned from chronic to myeloblastic type after phosphoramide therapy. Sykes (21) reported no response in chronic myeloid leukemia with DEPA therapy, and Asua (1) recorded negative results in 3 patients on Thio-TEPA therapy.

Wright and associates have released three reports on the control of chronic myelocytic leukemia with phosphoramides. In 1955 (25), they described one complete remission on TEPA and, in 1957 (26), they classified the response of 2 patients on Thio-TEPA as moderate; the next year (27), they reported 2 more remissions on Thio-TEPA as fair, lasting to 28 days. Farber (3) induced an 8 weeks' remission in one patient on TEPA. McIver (10) employed OPSPA to secure an objective remission in one case. In further studies, Farber (18, 19) noted some brief responses in patients with chronic myeloid leukemia following Thio-TEPA therapy, and Smith (20) added 3 more brief clinical remissions with this chemical.

* Furman University, Greenville, South Carolina.

Chronic Lymphocytic Leukemia. Chronic lymphoid leukemia has been tested almost as frequently with phosphoramides as has chronic myeloid leukemia. Leonard (7) induced 6 good clinical and hematologic remissions in 8 patients with Thio-TEPA, and Shay (17) reported similar satisfactory results in 5 of 7 cases. Winkler noted improvement in the peripheral blood picture in 3 of 5 patients and he concluded that phosphoramides were a mild agent in the therapy of leukemia. Wright (27) obtained remissions to 6½ months in 2 patients on Thio-TEPA, and Zarafonetis (28, 29) reported fair remissions, clinically and hematologically, in 2 patients on the same drug. Sykes (22) secured a 5 weeks' clinical remission in one patient with Thio-TEPA, and Olsen (12) noted an objective remission in one case on this therapy. McIver (10) described an objective remission in one patient with chronic lymphoid leukemia following administration of OPSPA, and Hunter (4) reported some response with Thio-TEPA.

Acute Leukemia. A number of clinical trials have been made in the management of acute leukemia with phosphoramides, but the results leave much to be desired. Farber (3) reported no benefit in 11 patients on TEPA; Smith (20) noted only brief clinical response in 12 patients following the use of Thio-TEPA and he indicated the chemical may have hastened the death of some patients. Shay (18) found Thio-TEPA without effect on acute leukemia. Some objective remissions were described by Koyama (6) in 2 of 3 patients following the use of Thio-TEPA. Sykes (21) obtained a remission of 2 weeks in a patient on DEPA, but he reported no response in a patient on Thio-TEPA.

Chronic Granulocytic Leukemia. In two reports on clinical trials with Thio-TEPA in granulocytic leukemia, Zarafonetis (28, 29) described clinical and/or hematologic response in all 9 patients and there were no undesirable side effects. Hunter (4) classed as "good" the response of his patients on Thio-TEPA therapy. This chemical caused the formation of obstructive uric acid crystals in a patient of McCrea (9).

Chronic Monocytic Leukemia. Shay (17) reported a limited response in one of 3 patients with chronic monocytic leukemia after Thio-TEPA therapy.

Summary

Four different phosphoramides, TEPA, DEPA, Thio-TEPA, and OPSPA, induced 87 remissions in 121 patients with 5 types of leukemia. Eighty per cent of the trials were with the one phosphoramide, Thio-TEPA. The response with the several types of leukemia to phosphoramide therapy was: 29 remissions in 41 chronic myeloid leukemia, 24 in 30 chronic lymphocytic leukemia, 15 of 28 acute leukemia, 18 of 19 chronic granulocytic leukemia, and 1 of 3 chronic monocytic leukemia.

Acknowledgments

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AMERICAN SOCIETY OF PHARMACOGNOSY

AT last summer's meeting of the Plant Science Seminar in Chicago, August 1959, the members in attendance approved the formation of a new society to be called the American Society of Pharmacognosy. [The organization of this society had been suggested the year before at the annual meeting of the Plant Science Seminar in Big Rapids and had been discussed during the time between meetings.]

The new Society according to its approved constitution is committed "to formalize and perpetuate the standard ideals of the Plant Science Seminar."

Its specific purposes are "to promote the growth and development of pharmacognosy, to provide the opportunity for association among workers in that science and in related sciences, to provide opportunities for presentation of research achievements and to promote the publication of meritorious research."

The newly-elected officers are:—

President ..... Varro E. Tyler, Jr.
(University of Washington)

Vice-President ..... Norman R. Farnsworth
(University of Pittsburgh)

Secretary ..... Frank L. Mercer
(St. Louis College of Pharmacy and Allied Sciences)

Treasurer ..... Frank A. Crane
(University of Illinois)

Executive Committee:

Edward P. Claus (Ferris Institute) ..... 1 Year
Carl H. Johnson (University of Florida) ..... 2 Years
David Carew (State University of Iowa) ..... 3 Years

MARIN S. DUNN,
Director, School of Biology, Philadelphia
College of Pharmacy and Science.

SELECTED ABSTRACTS

The Decomposition of Medicinals as a Result of Ingredients Combined With Them and Their Containers. Whittet, T. D. Symposium on Drug Stability at the 19th International Congress of Pharmaceutical Sciences, Zurich, Switzerland, Sept. 9, 1959. The author presented an extensive review of the incompatibilities encountered with excipients (defined for this review as any substance used in the formulation of a medicinial) and containers.

General incompatibilities were considered first. The direct oxidation of compounds such as adrenaline is accelerated by metallic ions and an alkaline pH. Sodium metabisulfite alone will not prevent this reaction but combination with a chelating agent is more effective. The antibiotics exhibit several reactions. Bacitracin is incompatible with several ointment bases and neomycin is incompatible with hydrous lanolin, anionic substances, and metallic ions. Penicillin has many incompatibilities and the tetracyclines are very susceptible to changes in pH and to metallic ions. Vitamins also exhibit numerous incompatibilities with pH changes, oxidation, metallic ions, and, in a few instances, with the sulfite group of antoxidants.

Noting some of the incompatibilities encountered with tablets and capsules, the author stated that calcium phosphate may cause an increase in the toxicity of calciferol. Monosaccharides and metallic ions are incompatible with aminophylline. A factor stressed by the author was that the excipient of tablets must not interfere with the distintegration or the absorption of the medicinal. Disintegration of a tablet is not a sufficient guarantee of availability for absorption. Both must be considered and inadequate consideration of either would constitute a form of incompatibility.

In solutions for injection, the author found that dextrose will react with local analgesics during autoclaving to form glycosides having little or no analgesic properties. Sodium para-aminohippurate also reacted with dextrose to form a glycoside that gave a false renal function reaction. Inert gas flushing of ampuls with carbon dioxide containing solutions of sodium aminosalicylate and of menadione sodium bisulfite seemed to accelerate decomposition rather than retard it.

In considering the relationship of containers to stability, the author discussed the liberation of metal ions and alkalizing substances from glass containers, the deleterious effects of various types of metal containers on products, and the problem of vapor transfer and the liberation of constituents from plastic and rubber containers and closures.

Increased Antibacterial Activity of Neomycin in the Presence of Certain Steroids. Wilkins, J. R. *Antibiot. & Chemother. 9*:464 (1959). In preliminary screening procedures, it had been found that certain microorganisms appeared to be more sensitive to neomycin sulfate in the presence of certain steroids. Of the gram-positive and gram-negative organisms used, only micrococci and streptococci showed significant potentiation of activity. In this particular study, several strains of *Micrococcus pyogenes* var. *aureus* and *Streptococcus hemolytics* were employed.

In vitro testing was undertaken. In the presence of 2.0 mg./ml. of the free alcohol or the hemisuccinate sodium esters of cortisone, hydrocortisone, and Δ′ hydrocortisone, it required approximately 10 to 50 times less neomycin to inhibit strains of these two bacteria. Acetates of the steroids were ineffective in potentiating antibiotic activity. In one series of experiments, 1 mcg./ml. of neomycin B was bacteriostatic against *M. pyogenes* var. *aureus*. However, upon the addition of 3.3 mg./ml. of hydrocortisone-21-hemisuccinate sodium to the solution, the same concentration of neomycin became bactericidal. It was also noted in this series that the ratio of steroid to neomycin was critical, for concentrations of more or less than 1 mcg./ml. of neomycin did not produce a bactericidal effect. Another observation noted was that the phenomenon did not require the simultaneous presence of steroid and antibiotic. If neomycin were added at zero time and the steroid within 4 hours, a bactericidal effect was obtained. If the reverse order was employed or if both components were added after four hours of incubation, a bacteriostatic and not a bactericidal effect was obtained. In general, it required approximately 1000 times more steroid than neomycin to demonstrate potentiation of the antibacterial activity.

A New Intramuscular Preparation of Oxytetracycline. Weinstein, H. J., Lidsky, S., and Delahunt, C. S. *Antibiot. Med. & Clin. Ther. 6:*526 (1959). The tetracycline antibiotics have been available for intramuscular injection only in the form of dry powders which had to be reconstituted just prior to administration. This limited the intramuscular use of these antibiotics largely to hospital conditions. Recently, an ethanolammonium magnesium salt of oxytetracycline has been developed which, when dissolved in a vehicle of 80 per cent propylene glycol in water, has been found to be stable. The solution is prepared by reacting proper molar ratios of oxytetracycline, a magnesium salt, and an alkanolamine in the propylene glycol-water vehicle. Two per cent lidocaine and an antoxidant are included and the preparation is maintained under an inert gas atmosphere.

The authors reported comparative stability studies on several lots of the new preparation after storage up to 3 months at both 37° C. and 50° C. Full potency was maintained in all lots reported after three months at 37° C. but there was a loss of about 20 per cent in potency after 3 months at 50° C. The authors stated that satisfactory projected potency retention for a period of 24 months was indicated by the studies.

Laboratory studies in rabbits showed that the blood levels obtained following intramuscular injection of the new preparation and an equivalent dose of a solution of the dry form of oxytetracycline were comparable. Intramuscular irritation studies were performed in rabbits using the new preparation and a tetracycline phosphate complex. The evaluation involved a single injection into the gluteal muscle followed in 24 hours by sacrifice of the animal and an examination of the muscle tissue. Gluteal muscle injections were also performed for 5 consecutive days, followed by sacrifice of the animal and evaluation of the muscle tissue. Following single injections, the authors reported that the new preparation produced no hemorrhagic lesion and only mild induration with little residual antibiotic while the phosphate complex showed hemorrhagic lesions in one-half of the animals and mild induration with appreciable residual antibiotic. Multiple injections showed an accentuation of these findings with evidence that the new preparation produced less tissue irritation and was more completely absorbed.

Clinical studies were also reported by the authors. In comparative tests, the new preparation was compared with commercially

available tetracycline preparations. In all cases, the new preparation was better tolerated both at a 100 mg. and a 250 mg. dosage level. In addition, satisfactory blood levels were attained and maintained for at least 12 hours. In a study of 303 patients given the new preparation, 77 per cent experienced no pain and only 1 per cent complained of marked pain.

Release of Drugs From Sustained Release Pelleted Preparations. Shenoy, K. G., Chapman, D. G., and Campbell, J. A. *Drug Standards 27:77* (1959). The Food and Drug Laboratories of Canada were interested in studying the evaluation of sustained-release preparations. The authors compared the results obtained from *in vitro* methods of the F. D. A., the A. M. A. Laboratories, and the F. D. L. with *in vivo* evaluations of urinary excretion rate and physiological availability in nine healthy male volunteers. The drug chosen for study was amphetamine in eight commercially available pelleted preparations labelled as being sustained-release type. For each subject, data were obtained on the blank urinary excretion prior to the ingestion of the drug, on the urinary excretion following the ingestion of the pure drug taken in solution in both the *d*- and *dl*-forms, and on the urinary excretion following the ingestion of the sustained-release capsules containing amphetamine. The urinary excretion, following administration of the pure drug, in comparison to the amount of pure drug taken in solution was considered to be a measure of the availability of the drug in the body.

The *in vivo* results indicated that *d*-amphetamine sulfate was excreted, following ingestion of the pure form, to the extent of 52.2 per cent while *dl*-amphetamine sulfate was excreted to the extent of 69.8 per cent within 56 hours. From 14.6 to 55.4 per cent of the dosages taken in the *d*-form in the pelleted products was recovered in the urine, corresponding to an availability of 28 to 106 per cent on the assumption that the 52.2 per cent of the standard excreted was equivalent to 100 per cent availability. The availability of the *dl*-form from one pelleted product was 101 per cent.

The *in vivo* results of studies of the rate of excretion were presented in table and graph form. Two of the products containing the *d*-form were totally available but showed no sustained-release effect.

Two other products were not totally available and did not show a sustained-release effect. The three other products containing the *d*-form showed sustained-release effect over about 20 hours but one showed a low availability. The eighth pelleted product contained the *dl*-form and was fully available and exhibited sustained-release over about 24 hours.

The *in vitro* methods used, although varying considerably in technique, were found to give comparable release of the drug from the pelleted preparations. They distinguished clearly between products which were grossly different in make-up but were not capable of making fine distinctions.

In conclusion, the authors stated that only two of the pelleted preparations exhibited sustained-release effect by showing an extended rate of excretion and by being fully available. In comparison with *in vitro* testing, the authors concluded that it should be possible to mix different proportions of pellets of varying disintegration times and determine quite precisely what amount of *in vitro* released drug constitutes sustained-release *in vivo* and what does not. The authors felt that these are the limits that must be defined in any *in vitro* test and that urinary excretion data would be useful in standardizing such tests which, by themselves, are meaningless.

The Detection of Particles in Solutions in Ampuls. Graham, W. D., Chatten, L. G., Pernarowski M., Cox, C. E., and Airth, J. M. *Drug Standards 27*:61 (1959). A collaborative study was undertaken to learn more about the status of plant inspection of ampuls, to learn something of the factors which influence the adequacy of inspections, and to determine whether or not individual inspectors with relatively little, extensive, or sporadic experience could perform an adequate inspection of ampuls to detect the presence of extraneous particles. The study was undertaken by a Food and Drug Laboratory and three pharmaceutical manufacturing laboratories. Sixty ampuls were obtained from the regular production from each of three pharmaceutical manufacturers in each of three sizes; *i.e.*, 1 ml., 5 ml., and 10 ml.

Following the inspections and analysis of the results, it was found that 12 individual inspectors—3 each from 4 different locations—

agreed with their own previous decisions as to whether or not an ampul should be rejected 64 to 83 per cent of the time when the ampuls contained clear, aqueous solutions. Usually, when an inspector found a high percentage of rejects, he found it more difficult to obtain a high level of self-agreement. This was probably due to the fact that many of the particles found were at the limits of detection. Inspectors from drug manufacturing plants were found to work at a faster rate than the essentially inexperienced inspectors at the Food and Drug Laboratory but they found about one-third less rejects.

A comparison of the inspection results with those originally claimed by the manufacturers showed that the inexperienced inspectors found about 18 per cent more rejects than claimed while all other inspectors found 25 per cent less than claimed. Most of the variation found among the results obtained by experienced inspectors seemed to reside within the individual concerned and did not appear to be influenced to any marked degree by the equipment and technique employed.

An interesting finding reported was that no evidence was found to support the belief that, over a prolonged period, the number of rejects in a given lot of ampuls tends to increase. Also, in this series, the 10 ml. size of ampul was found to have the smallest number of rejects and the 1 ml. size, the largest number.

In conclusion, the authors stated that it would appear to be possible to inspect ampuls containing clear, aqueous solutions with a reproducibility having a variation of approximately 15 per cent of the reported number of rejects.

Premenstrual Tension Controlled With Meprobamate and a Diuretic. Podolsky, E. *The J. Lancet 79*:318 (1959). A group of 100 unselected cases of women with premenstrual tension who were between the ages of 22 and 40 were given medication during the ten days prior to the onset of menses. The drug regimen was as follows during four months of the study: (1) Ammonium chloride alone was prescribed in a dose of 0.5 Gm. twice daily during the first month, (2) Ammonium chloride alone was repeated to 90 patients while the remaining 10 patients also received 400 mg. of meprobamate three

times a day, (3) The third month all patients received the ammonium chloride and 400 mg. of meprobamate four times a day, and (4) All patients received the ammonium chloride and a lactose placebo in place of the meprobamate during the fourth month.

The results were found to be striking. Meprobamate completely or substantially relieved symptoms of anxiety and tension in 86 of the 100 women studied. Adequate emotional control was achieved by all of the women. Ability to function at daily activities improved substantially. Among 52 women who were gainfully employed, an average of about 1200 working hours a month were lost prior to therapy. During therapy with meprobamate and the diuretic, only one woman lost 24 working hours. Participation in social activities was found to improve, but not dramatically. The age of the patient did not significantly influence the response to therapy. Following the withdrawal of meprobamate and substitution of the lactose placebo, every patient exhibiting a favorable response to the drug reverted to her original anxiety pattern and emotional status. This strongly suggested that any decrease in premenstrual tension resulted from meprobamate rather than from diuretic therapy or other factors. However, the author felt that the diuretic assisted in restoring a proper water balance and was a valuable adjunct to therapy.

Administration of an Intravenous Fat Emulsion. Nell, E. R., and Gerber, M. L. *U. S. Armed Forces Med. J. 10*:811 (1959). Fat, because of its high caloric content per unit of weight, is an excellent source for intravenous administration of a maximum of calories with a minimum volume of necessary aqueous vehicle. The volume of water is the primary limiting factor for other sources of calories, such as carbohydrates and proteins. The relatively recent development of non-toxic emulsifying agents has made intravenous fat emulsions available and safe for administration to patients whose normal alimentary activity has been interrupted.

A series of 187 units of 500 ml. of a 15 per cent fat emulsion were administered to 69 surgical patients. Thirty-five patients received only one unit of the emulsion. Of the remaining 34 patients, four received more than 10 units each. The temperature, pulse, blood pressure, and subjective reactions were recorded.

Major reactions were immediate (usually occurring after only a few milliliters had been given) or delayed (usually occurring during the transfusion but might be delayed for a few hours). Major reactions consisted of chest or back pain, dyspnea, flushing, or urticaria. The delayed reaction was usually in the form of a chill. The minor reactions usually consisted of mild temporary fever, nausea, vomiting, abdominal discomfort, headache, and dizziness. Mild temporary fever was the most common side reaction, 15 cases showing an elevation of 2.0° F. or more. A total incidence of side reactions occurred in 24 cases.

The authors concluded that no significant complication arose from the intravenous administration of the fat emulsion. Immediate reactions are of a mild nature and are not sufficiently severe to preclude its clinical use over limited periods of time.

BOOK REVIEWS

Experimental Control of Plant Growth. Fritz W. Went. 596 pp. Chronica Botanica Company, Waltham, Mass., 1957.

This book is divided into three parts, each of which might conceivably be considered an entity in itself. However, the author has unified the work by developing a natural relationship among the parts.

Part I deals with the construction, maintenance, and operation of the Earhart Plant Research Laboratory at the California Institute of Technology. An entire chapter is devoted to the details of construction of the Laboratory's components: greenhouses; constant-temperature and artificial-light rooms; heating, refrigeration, air-conditioning, and electrical power systems; control room; and automatic CO_2-analyzer. In other chapters, emphasis is placed on reliability of environmental control and on maintenance of relative sterility. Attention is focused on methods of handling plants: moving, coding, record-keeping, measuring, and photographing.

Part II contains the results of experiments on the behavior of various plant species and varieties. All data are from experiments carried out in the Earhart Laboratory. Potential or actual economic importance admittedly was one of the factors determining the selection of a plant for investigation. Another determining factor was suitability of the species for solution of specific problems such as photoperiodicity, effects of smog, germination, tuber-formation, and vernalization. Other plants were selected specifically for studying ecological or genetic problems. Because of space limitations, perennial plants, especially trees and shrubs, are poorly represented in the experiments.

A discussion of general plant physiology and ecology is set forth in Part III. The facts and conclusions are restricted to the investigations conducted in the Earhart Laboratory. Typical of the problems discussed are photosynthesis, growth, nutrition, transpiration, genotypic and phentoypic variability, climatology, and growth hormones.

The author has included in Parts II and III contributions by W. C. Ashley, L. T. Evans, A. W. Galston, H. Hellmers, and W. M. Hiesey. An eight-page bibliography and twenty-five photographic plates are incorporated at the end of the text.

C. A. Apostolides

Modern Pharmacognosy. Egil Ramstad. 480 pp. Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y., 1958.

Previous textbooks in pharmacognosy have mostly followed the botanical or chemical classifications of the drugs and, although such a treatment of the subject has its own advantages, yet it leaves many questions unsolved. For example, such texts describe the chemical nature of the constituents but do not throw any light as to how, where, when, and why these constituents are being formed in any particular tissue or organ. Thus, the present work partially fulfills the long-standing need of a biogenetic classification of the drugs.

We are still far from knowing the exact biological processes going on within the living protoplasm of plant or animal cells and the factors involved in controlling such processes; nevertheless, in recent years, we have learned enough about these processes and factors to handle the crude drugs as biological entities, produced as a result of the activities of the living organism. The author is to be congratulated for presenting a rather difficult and controversial subject in a clear, logical, and easily understood manner.

In a book of this size, the matter could not have been handled in a better way. Except for the chapter on proteid group drugs which is rather wide in its coverage of various unrelated items, all other chapters are appropriate and well-written.

This is a very useful book and would be a valuable addition to the library of any pharmacognosist or biochemist.

C. A. Apostolides

Mechanisms of Hypertension: With a Consideration of Atherosclerosis. H. A. Schroeder. xv + 379 pp. Charles C. Thomas, Publisher, Springfield, Illinois, 1957. Price: $9.00.

When basic pathophysiological mechanisms which interact to produce a disease are studied and understood, specific therapy becomes possible. It was with this in mind that this monograph was assembled.

The author's familiarity and experience with hypertensive disease are manifest by the completeness and versatility of the presentation. The busy physician and pharmacist will appreciate the

discussion and commentary of the various therapeutic agents currently available and in use. The researcher's awareness of the dirth of information available about critical areas of this disease state is sharpened, while new avenues of approach are awakened in his mind. The logic for the use and the therapeutic limitations of each drug is examined with respect to its primary action.

In the final chapters, current concepts of the role of dietary factors, such as fats, vitamins, hormones, and trace metals are discussed. The controversial aspects of the part these substances have in both the hypertensive and atherosclerotic process is considered. Although universal agreement does not exist on the interrelations of hypertension and atherosclerosis, the author offers for comparison a thorough summary of the information on this problem.

Although published in 1957, the advanced thinking of this book will maintain for it a place as a timely reference for many future years.

THOMAS H. F. SMITH

Introduction to Public Health, Fourth Edition. Mustard, H. S., and Stebbins, E. L. 338 pages. Macmillan Company, New York, N. Y., 1959.

The title is descriptive of the text which has been designed to orient students in the field of public health. There is a consolidation of factual material within fifteen chapters. The subjects covered pertaining to public health are: its history and background, public health organization and administration, vital statistics, health education, personal hygiene, environmental health, communicable diseases and their specific programs, maternal and child health, pre-school and school health, chronic diseases and care.

The material is presented in an excellent and easily read form in the fourth edition of a text which first appeared twenty-five years ago. The authors have effectively revised the text to follow the dramatic changes that have occurred in public health since the appearance of their last revision (third edition) over six and one-half years ago.

The book is to be highly recommended as a primer for everyone interested in learning the principles of public health.

BERNARD WITLIN

Disease Detectives. Harry Edward Neal. 192 pp. Julian Messner, Inc., 8 W. 40th Street, New York 18, N. Y. Price: $3.50.

We are witnessing today an ever growing number of career booklets, magazine articles, books and other printed forms to tell younger folks, mostly in high school, of the opportunities that await them in the many fields from which they may choose their life work. Most of these vocational treatises are factual, many are interesting, but only as few are as fascinating as "Disease Detectives," subtitled "Your Career in Medical Research."

In 17 chapters, success stories are told in medicine, physiology, biochemistry, biology, pathology, mycology, mental health, nursing, dentistry, nuclear science, and engineering as related to medical research, pharmacology, and several other specialties. It is to be regretted that so little space is devoted to the practicing pharmacist, who is fully entitled to a more elaborate vocational guidance treatment than received here.

The author has written several other career books. His style is adult, yet fluid enough to attract the attention of the younger generation, and to keep it. There is a center spread of attractive illustrative pictures, a complete index, a bibliography, and a good list of sources of further information.

JOHN E. KRAMER

Ataractic and Hallucinogenic Drugs in Psychiatry. World Health Organization Technical Report Series No. 152. 72 pp. World Health Organization, Geneva, Switzerland, 1958. Price: $0.60.

This report summarizes the great strides made in the study of the action, and the mode of action, of drugs on mental function in man. In addition to presenting the clinical significance of ataractics, this work also summarizes and correlates such vital experimental tools as the science of animal behavior, trends in neurological sciences, and the anatomical relationships of the central nervous system.

The most outstanding feature of this booklet is the two tables which summarize the experimental and clinical features of the various ataractic agents.

This booklet makes for easy and enjoyable reading, and should be included in the library of all scientists engaged in the study of mental health.

E. E. VOGIN

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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